

Remarks

Claims 1, 2, 6, 7, 9, 11-13, 17-19, and 21-24 were pending in the subject application. By this Amendment, claim 11 has been amended, and claim 24 has been cancelled. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Claims 6, 7, 9, 18, 19, 21, and 23 remain pending but withdrawn from consideration. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 1, 2, 11-13, 17, and 22 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants and the applicants' representative wish to thank Examiner Lockard for the courtesy of the telephonic interview conducted with the undersigned on August 29, 2006, regarding the written restriction requirement.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application.

The applicants gratefully acknowledge the Examiner's indication that claims 1, 2, 12, 13, 17, and 22 are allowable.

The applicants note that claim 8 is listed as currently pending on the Office Action Summary page. Claim 8 was cancelled in the applicants' Preliminary Amendment submitted on March 21, 2005.

Claims 11 and 24 are rejected under 35 U.S.C. §101 on the grounds the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The applicants respectfully submit that the claimed invention is supported by a specific and substantial utility.

At page 4, the Office Action acknowledges that the isolated human sphingosin 1-phosphate receptor (SPPR) nucleic acid sequence set forth as SEQ ID NO:4 has utility, for example, as a probe for the diagnosis of large granular lymphocyte (LGL) leukemia. However, the Office Action indicates that the SPPR polypeptide (SEQ ID NO:3) is not supported by a specific and substantial

utility because the specification does not disclose any disorders that are associated with altered levels or forms of the SPPR polypeptide. As disclosed at page 2, lines 19-21 and 27-29, and claims 6-8, of the subject application as filed, the present inventors found that *sppr* gene is over-expressed in LGL leukemia patients compared to normal individuals, and the invention includes a method for screening for autoimmune diseases, including LGL, based on over-expression of the *sppr* gene. The *sppr* gene and S1P5 are referred to interchangeably, as indicated at page 3, lines 12-14, of the specification. Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Thomas P. Loughran, Jr., an inventor of the subject invention. Submitted with the Declaration as Exhibit B is a Western blot of lysates from peripheral blood mononuclear cells (PBMC) from patients suffering from large granular lymphocyte (LGL) leukemia (labeled LGL1 and LGL2) and from normal individuals (labeled N1 and N2), along with the materials and methods utilized. As indicated in Dr. Loughran's Declaration, the S1P5 polypeptide (also referred to in the subject application and herein as SPPR), is elevated in patients suffering from LGL compared to normal individuals, which is consistent with the microarray data provided in the subject application. Thus, "it is reasonable to conclude that an elevated level of S1P5 mRNA or protein in PBMC correlates with LGL leukemia, and is useful as a diagnostic marker of the disease".

The applicants have disclosed a specific utility for the claimed invention and provided a credible basis supporting that specific utility. One skilled in the art would conclude that the S1P5 polypeptide has a specific utility as a diagnostic marker of LGL leukemia, which is ready to use, in a real-world application. For example, the S1P5 polypeptide may be used to produce monoclonal antibodies for use in immunoassays for the detection of S1P5 polypeptide in PBMC or other samples, as embraced by claims 6 and 8 of the application as originally filed. Thus, the method for making the S1P5 polypeptide recited in claim 11 also has utility. Claim 24 has been cancelled. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §101 is respectfully requested.

Claims 11 and 24 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the specification enables one of ordinary skill in the art to make and use the invention without undue experimentation.

As indicated above, the applicants have submitted evidence supporting the utility of the S1P5 polypeptide as a diagnostic marker of LGL leukemia. In addition, by this Amendment, the applicants have amended claim 11 to refer to the nucleic acid molecule of claim 2, which comprises SEQ ID NO:4. Claim 11 no longer refers to the complement of SEQ ID NO:4. The method of claim 11 has been established to be both useful and operative. Claim 24 has been cancelled. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

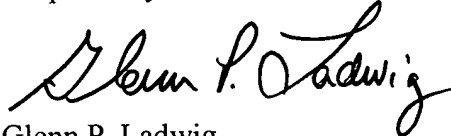
Claim 11 is rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that the claim is not indefinite. However, as indicated above, the applicants have amended claim 11 to refer to the nucleic acid molecule of claim 2, which comprises SEQ ID NO:4. Thus, the claim apprises one of ordinary skill in the art of its scope. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Request for Continued Examination
Petition and Fee for Extension of Time
Declaration under 37 C.F.R. 1.132 by Dr. Thomas P. Loughran, Jr.
Exhibits A and B

EXHIBIT A

CURRICULUM VITAE

Name: Thomas P. Loughran, Jr., M.D.
196-42-2149

Birth date: November 12, 1953

Birthplace: Darby, Pennsylvania

Citizenship: U.S.A.

Education:

1975 B.S.; Ursinus College, Collegeville, Pennsylvania (Biology)

1979 M.D.; Hahnemann Medical School, Philadelphia, Pennsylvania

Research and Professional Experience

1979 - 1982 Internal Medicine Internship and Residency, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

1982 - 1985 Senior Oncology Fellow, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA

1983 - 1985 Transplantation Biology Division, Fred Hutchinson Cancer Research Center, Laboratory of Dr. Rainer Storb

1985 - 1986 Associate in Clinical Research, Fred Hutchinson Cancer Research Center, Seattle WA

1986 - 1990 Assistant Member, Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA

1990 - 1992 Associate Member, Clinical Research, Fred Hutchinson Cancer Research Center, Seattle WA

10/86 - 1/87 Visiting Scientist, National Cancer Institute- Frederick Cancer Research Facility, Laboratory of Dr. Francis Ruscetti, Frederick, MD

1992 - 1996 Professor of Medicine and Microbiology and Immunology
Associate Director, Bone Marrow Transplant Program SUNY Health Science Center and Chief of Hematology, Veteran's Administration Medical Center, Syracuse, NY

1996 - 2003 Program Leader, Hematologic Malignancies
H. Lee Moffitt Cancer Center and Research Institute
Professor of Medicine
University of South Florida
Tampa, FL

2003 – Present Director, Penn State Cancer Institute
Professor of Medicine
Penn State College of Medicine
Hershey, PA

Honors and Awards:

1975	B.S. <u>cum laude</u> , Departmental Honors (Biology), Ursinus College Sigma XI National Research Honor Society; Cub and Key Honor Society, Ursinus College
1976	Honors for Basic Sciences curriculum (top 10% of class), Hahnemann Medical School
1979 - 1980	Intern of the Year, Thomas Jefferson University Hospital
1983 - 1984	American Cancer Society Clinical Fellow
1985 - 1987	Fellow of the Leukemia Society of America
1987 - 1990	Special Fellow of the Leukemia Society of America

Major Research Interests

LGL leukemia, Hematologic Malignancies

<u>Licensure:</u>	1980, 2003 Pennsylvania	MD023733-E
	1982 Washington	MD19856
	1992 New York	189155
	1996 Florida	ME0077296

Board Certification

1982	Diplomat, American Board of Internal Medicine
1985	Diplomat, Oncology Subspecialty, American Board of Internal Medicine

Board Eligible: 1985 Hematology

Publications:

1. **Loughran TP, Jr**, Kadin ME, Starkebaum G, Abkowitz JL, Clark EA, Distech C, Lum LG, Slichter SJ: Leukemia of large granular lymphocytes: Association with clonal chromosomal abnormalities and auto-immune neutropenia, thrombocytopenia and hemolytic anemia. Ann Intern Med., 102:169-175, 1985.
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5. **Loughran TP, Jr**, Deeg HJ, Storb R: Morphologic and phenotypic analysis of canine natural killer cells: Evidence for T-cell lineage. Cell Immunol, 95:207-217, 1985.
6. Wallis WS, **Loughran TP, Jr**, Kadin ME, Clark EA, Starkebaum GA: Polyarthritis and neutropenia associated with circulating large granular lymphocytes. Ann. Intern. Med., 103: 357-362, 1985.
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8. **Loughran TP, Jr**, Kadin ME, Deeg HJ: T-cell intestinal lymphoma associated with celiac sprue. Ann. Intern. Med., 104:44-47, 1986.
9. Deeg HJ, Doney K, Sullivan KM, **Loughran TP, Jr**, Appelbaum F, Kennedy M, Witherspoon RP, Storb R: Antithymocyte globulin followed by cyclosporine for the treatment of acute GVHD in patients given HLA-identical or nonidentical marrow grafts. Transplant Proc, 18:791-793, 1986.
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12. **Loughran TP, Jr**, Clark EA, Price TH, Hammond WP: Adult onset cyclic neutropenia is associated with increased large granular lymphocytes. Blood, 68:1082-1087, 1986.
13. Sullivan KM, Witherspoon R, Deeg HJ, Doney K, Appelbaum F, Sanders J, Lum L, **Loughran TP, Jr**, Hill R, Anasetti C, Shields A, Nims J, Shulman H, Storb R, Thomas ED: Chronic graft-versus-host disease in man. Bone Marrow Transplantation, UCLA Symposia on Molecular and Cellular Biology, 53:473-487, 1987.
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51. Aprile JA, Russo M, Pepe MS, **Loughran TP, Jr**: Activation signals leading to proliferation of normal and leukemic CD3+ large granular lymphocytes. Blood 78:1282-1285, 1991.
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Research Support:

Past Support

- | | |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1985-1987 | Fellow in the Leukemia Society of America
"Natural Killer Cells: Studies in Patients with Leukemia & Large Granular Lymphocytes"
\$20,000 direct costs annually |
| 1986-1987 | Short Term Scientific Exchange Award, Leukemia Society of America
\$5,000 direct costs annually |
| 1987-1990 | Special Fellow of the Leukemia Society of America
"Molecular Immunology of LGL Leukemia"
\$30,000 direct costs annually |
| 1986-1987 | P.I., Leukemia Research Foundation
"Molecular Immunology of LGL Leukemia"
\$35,000 direct costs annually |
| 1987-1988 | P.I., Leukemia Research Foundation
"Studies on the Pathogenesis of LGL Leukemia"
\$35,000 direct costs annually |
| 1986-1991 | P.I., Project 4 NCI PO1 grant awarded to R. Storb
"Studies in Marrow Graft Resistance"
\$120,000 direct costs annually |
| 1989-1991 | P.I., American Cancer Society research grant CH-457
"Molecular Immunology of LGL Leukemia"
\$80,000 direct costs annually |
| 1990-1994 | P.I., NCI RO1 grant CA 46903
"Studies of LGL Leukemia"
\$136,692 direct costs annually |
| 1991-1995 | P.I., NCI RO1 grant CA 54552
"Retroviral Infection in LGL Leukemia"
\$86,214 direct costs annually |

1996-2000	P.I., VA Merit Review Grant "Pathogenesis of LGL Leukemia" \$99,000 direct costs annually
1999 – 2001	P.I., NCI R21 Grant CA 78724 "Dyregulation of Apoptosis in LGLLeukemia" \$100,000 direct costs annually
2000 – 2005	NCI PO1 Grant CA 82533 "Molecular Oncology Program Project" Project III, Co-PI \$166,700 direct costs annually
2000 – 2003	P.I., Hisamitsu Pharmaceuticals "Gene Discovery in Rheumatoid Arthritis" \$100,00 direct costs annually
2001-2004	NCI RO1 Grant CA90717 "Arsenic Based Therapy of BcrAbl Positive Leukemias" Co-P.I. \$250,000 direct costs annually
2002 – 2007	P.I., NCI K12 CA 87989 "Clinical Scholars in Oncology" \$700,000 direct costs annually
2000 – 2005	P.I., NCI K24 Grant CA 83947 "Clinical Investigations in LGL Leukemia" \$108,125 direct costs annually

Current Support

2000 – 2006	P.I., VA Merit Review Grant "Pathogenesis of LGL Leukemia" \$144,500 direct costs annually
2001-2006	P.I., NCI RO1 Grant CA90633 "Therapeutic Response in LGL Leukemia" \$207,500 direct costs annually
2003-2008	P.I., NCI R01 Grant CA94872 "Survival Mechanisms in Leukemic NK Cells" \$222,500 direct costs annually
2003-2008	P.I., Penn State Consortium of NIH U54 Application RR01 Grant 9397 "Bone Marrow Failure Clinical Research Center" \$108,353 direct costs annually
2005-2009	P.I., Penn State Subcontract Co-P.I., NCI R01 Grant CA112112 "Targeted Drug Therapy for LGL Leukemia" \$55,344 direct costs annually

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EXHIBIT B

Control	N1	N2	LGL 1	LGL 2
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S1P5 —



Western blot of S1P5 in PBMC of patients suffering from LGL leukemia

Peripheral blood mononuclear cells (PBMC) were isolated from human patient blood and from normal donor controls. Cells were lysed in radio-immunoprecipitation assay (RIPA) buffer containing phosphatase and protease inhibitors (phenylmethylsulfonyl fluoride (PMSF), leupeptin, and sodium vanadate). The proteins were quantified according to the Bradford Assay (Bradford, M. M., *Anal. Biochem.*, 1976, 72:248-254), and loaded equally on to 10% polyacrylamide gels. Lane 1 is a lysate from a cell line expressing S1P5 protein (positive control). Lanes 2 and 3 are lysates from PBMC of normal individuals (N1 and N2). Lanes 4 and 5 are lysates from PBMC of patients with large granular lymphocyte (LGL) leukemia.

Proteins were electrophoresed at 150 volts and transferred to nitrocellulose membranes (BioRad semi-dry blotter). Membranes were blocked with 5% Carnation non-fat dry milk for 30 minutes, and incubated with rabbit polyclonal antibody to S1P5 (EDG-8, Exalpha Corp, Boston, MA). The blots were washed 3X in PBS-Tween and incubated for 1 hour with anti rabbit secondary antibody. Blots were then washed and developed using the ECL Plus chemiluminescent system (Amersham). The blots were exposed to Omat-X AR film (Kodak).